IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:	)	
	)	
Jens PETERSEN	)	Examiner: Blessing M. Fubara
	)	
Serial No.: 09/938,667	)	Group Art Unit: 1615
	)	
Filed: August 27, 2001	)	

For: POLYACRYLAMIDE HYDROGEL FOR THE TREATMENT OF INCONTINENCE AND VESICOURETAL REFLUX

REQUEST FOR EXTENSION OF TIME AND
RESPONSIVE AMENDMENT UNDER 37 C.F.R. § 1.111

Director of the United States Patent and Trademark Office
Washington, D.C. 20231

Sir:

REQUEST FOR EXTENSION OF TIME

Applicant respectfully requests a two-month extension of time under 37 C.F.R. § 1.136(a) for responding to the Office Action mailed on March 13, 2002, in the above-captioned patent application. Accordingly, it is respectfully requested that the time for response be extended up to and including August 13, 2002. Please find a check in the amount of $400.00 to cover the two-month extension of time fee. In the event of any variance between the above amount and the fees determined by the U.S. Patent and Trademark Office, please charge or credit any such variance to the undersigned's Deposit Account No. 50-0206.

AMENDMENT/RESPONSE

The Office Action mailed March 13, 2002, has been received and carefully considered. In response to the Office Action, please consider the below comments and amendments.

Claims 1-19 are currently pending in this application, following this amendment claims 1-47 will be pending. The specification has also been amended to correct minor informalities. A marked up version of the specification and claims is enclosed in Attachment A. No new

matter is added by the amendment. Insertions are indicated by underline and deletions are indicated by strikethrough.

Further please amend the specification as follows:

IN THE SPECIFICATION:

I. On Page 1, lines 6-10, please delete the paragraph and replace it with the following replacement paragraph.

Polyacrylamide hydrogels are used herein as endoprosthetic devices for bulking the urethra, rectum or colon (or *canalis analis*), or ureter in order to increase resistance in these conduits for the treatment of urinary incontinence, anal incontinence, and vesicouretal reflux. The polyacrylamide hydrogels comprise 0.5 to 25% by weight polyacrylamide and either pyrogen-free water or saline solution.

II. On Page 1, lines 26-31, please delete the paragraph and replace it with the following replacement paragraph.

Vesicouretal reflux is the result of decreased ureteral resistance wherein urine from the bladder refluxes back into the kidney. This can result in the transport of bacteria from the bladder back up through the ureter, clayceal dilation, the renal pyramids and the kidneys and may lead to infections and recurrent pyelonephritis as well as cause physiological injury to the renal parenchyma. This may lead to renal failure.

III. On Page 3, lines 21-25, please delete the paragraph and replace it with the following replacement paragraph.

A first aspect of the invention relates to a bio-stable hydrogel for use in the treatment and prevention of incontinence and vesicouretal reflux, said hydrogel obtainable by combining acrylamide and methylene bis-acrylamide in amounts so as to give about 0.5 to 25% by weight polyacrylamide, based on the total weight of the hydrogel; radical initiation; and washing with pyrogen-free water or saline solution.

IV. On Page 4, lines 1-5, please delete the paragraph and replace it with the following replacement paragraph.

An important object of the invention is to provide a prosthetic device for increasing the resistance of conduits selected from the group consisting of the urethra; the rectum or colon; and the ureter for the treatment of urinary incontinence, anal incontinence, and vesicouretal reflux,

respectively; wherein said device is injectable and comprises the bio-stable hydrogel of the invention.

V. On Page 4, lines 11-22, please delete the paragraph and replace it with the following replacement paragraph.

A first aspect of the invention relates to the bio-stable hydrogel obtainable by combining acrylamide and methylene bis-acrylamide in amounts so as to give about 0.5 to 25% by weight polyacrylamide, based on the total weight of the hydrogel; radical initiation; and washing with pyrogen-free water or saline solution, for use in the treatment and prevention of incontinence and vesicouretal reflux. The bio-stable hydrogel typically has a molecular weight between 0.01 x 10^6 and 20 x 10^6. The polymer is resistant to biological degradation and is not permeable through biological membranes. The polyacrylamide hydrogel of the invention is fully biocompatible (according to ISO standard test ISO-10993). The polyacrylamide hydrogel does not have cytotoxic effect on human fibroblasts, is non-toxic, non-carcinogenic, non-allergenic, non-mutagenic, and resistant to enzymatic and microbiological degradation. Furthermore, the polymer is not water-soluble.

VI. On page 5, lines 26-30, please delete the paragraph and replace it with the following replacement paragraph.

The device also has elastic properties due to, at least in part of the high water binding capacity of the hydrogel of water. This is of great relevance in terms, at least, of durability and ability to provide resistance through the conduit. In a preferred embodiment, the hydrogel of the invention has an elasticity modulus of about 1 to 200 Pa, such as about 2 to 175 Pa, typically about 5 to 150 Pa, such as 10 to 100 Pa.

VII. On page 14, line 10, please delete the paragraph and replace it with the following replacement paragraph.

g) pre-wash values - washing typically reduces value by 20-40%

VIII. On page 17, lines 1-5, please delete the paragraph and replace it with the following replacement paragraph.

The medical procedure involves injection of polyacrylamide gel under the mucous membrane of the uretha of women suffering from incontinence. Injection is via the external surface of the urethra and toward the submucosal membrane. 3 mL are injected at three depots

sites made along a single longitudinal position of the urethra. Depots 0.5 cm distally from the neck of the bladder were made.

In accordance with 37 C.F.R. § 1.121(b), also enclosed, in Appendix A, is a version of the above replacement paragraphs marked-up to show all the changes relative to the deleted paragraphs. The specification has been amended to correct minor informalities and typographical errors.

In the Claims:

Please amend claims 1-9, 11-14, and 16-19, and add claims 20-47.

1. (Amended) A bio-stable hydrogel comprising the combination of acrylamide and methylene bis-acrylamide in amounts to provide about 0.5 to 25% by weight polyacrylamide, based on the total weight of the hydrogel wherein said biostable hydrogel is in a form suitable for the treatment of incontinence and vesicouretal reflux and is substantially free of monomeric units.

2. (Amended) The hydrogel according to claim 1, wherein said combination of acrylamide and methylene bis-acrylamide is obtained by combining the acrylamide and the methylene bis-acrylamide in a molar ratio of 150:1 to 1000:1.

3. (Amended) The hydrogel according to claim 1, comprising less than 15% by weight polyacrylamide, based on the total weight of the hydrogel.

4. (Amended) The hydrogel according to claim 1, comprising at least 1% by weight polyacrylamide, based on the total weight of the hydrogel.

5. (Amended) The hydrogel according to claim 1, having a complex viscosity of about 2 to 40 Pas.

6. (Amended) The hydrogel according to claim 1, for use in the treatment of incontinence.

7. (Amended) The hydrogel according to claim 42, further comprising at least 75% by weight pyrogen-free water or saline solution.

8. (Amended) The hydrogel according to claim 7 comprising at least 80% by weight pyrogen-free water or saline solution.

9. (Amended) A method of treating incontinence or vesicouretal reflux comprising administering a hydrogel to a mammal, said hydrogel comprising 0.5 to 25% by weight polyacrylamide, based on the total weight of the hydrogel and is substantially free of monomeric units.

11. (Amended) The method according to claim 9, wherein the hydrogel comprises less than 15% by weight polyacrylamide, based on the total weight of the hydrogel.

12. (Amended) The method according to claim 11, wherein the hydrogel comprises at least 1% by weight polyacrylamide, based on the total weight of the hydrogel.

13. (Amended) The method according to claim 9, wherein the hydrogel has a complex viscosity of about 2 to 40 Pas.

14. (Amended) The method according to claim 9, wherein the hydrogel comprises at least 80% by weight pyrogen-free water or saline solution.

16. (Amended) The method according to claim 15, wherein the injecting of the hydrogel comprises injections which include
injections at positions 10, 2, and 6 o'clock of the cross-sectional axis of the urethra for the treatment of urinary incontinence;
injections at positions 10, 2, and 6 o'clock of the cross-sectional axis of the colon or rectum for the treatment of anal incontinence; or
injections at positions 10, 2, and 6 o'clock of the cross-sectional axis of the ureter for the treatment of vesicouretal reflux.

17. (Amended) The method according to claim 9, further comprising the inclusion of cells.

18. A prosthetic device for increasing the resistance of conduits comprising a urethra, a rectum, a colon, or a ureter
wherein said device is injectable and comprises a hydrogel as defined in any of claims 1 to 8.

19. (Amended) The device according to claim 18, further comprising cells.

20. (New) The hydrogel according to claim 1, comprising less than 10% by weight polyacrylamide, based on the total weight of the hydrogel.

21. (New) The hydrogel according to claim 1, comprising less than 7.5% by weight polyacrylamide, based on the total weight of the hydrogel.

22. (New) The hydrogel according to claim 1, comprising less than 5% by weight polyacrylamide, based on the total weight of the hydrogel.

23. (New) The hydrogel according to claim 1, comprising less than 3.5% by weight polyacrylamide, based on the total weight of the hydrogel.

24. (New) The hydrogel according to claim 1, comprising at least 1.5% by weight polyacrylamide, based on the total weight of the hydrogel.

25. (New) The hydrogel according to claim 1, comprising at least 1.6% by weight polyacrylamide, based on the total weight of the hydrogel.

26. (New) The hydrogel according to claim 1, having a complex viscosity of about 2 to 30 Pas.

27. (New) The hydrogel according to claim 1, having a complex viscosity of about 2 to 20 Pas.

28. (New) The biostable hydrogel composition of claim 42, wherein washing is done with pyrogen-free water.

29. (New) The method according to claim 9, wherein the hydrogel comprises less than 10% by weight polyacrylamide, based on the total weight of the hydrogel.

30. (New) The method according to claim 9, wherein the hydrogel comprises less than 7.5% by weight polyacrylamide, based on the total weight of the hydrogel.

31. (New) The method according to claim 9, wherein the hydrogel comprises less than 5% by weight polyacrylamide, based on the total weight of the hydrogel.

32. (New) The method according to claim 9, wherein the hydrogel comprises less than 3.5% by weight polyacrylamide, based on the total weight of the hydrogel.

33. (New) The method according to claim 9, wherein the hydrogel comprises at least 1.5% by weight polyacrylamide, based on the total weight of the hydrogel.

34. (New) The method according to claim 9, wherein the hydrogel comprises at least 1.6% by weight polyacrylamide, based on the total weight of the hydrogel.

35. (New) The method according to claim 9, wherein the hydrogel has a complex viscosity of about 2 to 30 Pas.

36. (New) The method according to claim 9, wherein the hydrogel has a complex viscosity of about 2 to 20 Pas.

37. (New) The method according to claim 17, wherein the cells comprise stem cells.

38. (New) The method according to claim 17, wherein the cells allow for cellular engraftment to the surrounding tissue in the ureter, urethra or *analis canalis*.

39. (New) The device according to claim 19, wherein the cells include stem cells.

40. (New) The device according to claim 19, wherein the cells allow for cellular engraftment to the surrounding tissue in the ureter, urethra or *analis canalis*.

41. (New) The device according to claim 18, wherein the device increases the resistance of the urethra to treat urinary incontinence, increases the resistance of the rectum or colon to treat anal incontinence or increases the resistance of the ureter to treat vesicouretal reflux.

42. (New) The hydrogel according to claim 1 which is made under the conditions of radical initiation and washing with pyrogen-free water or saline solution.

43. (New) The hydrogel according to claim 42 comprising at least 85% by weight pyrogen-free water or saline solution.

43. (New) The hydrogel according to claim 1 comprising at least 90% by weight pyrogen-free water or saline solution.

45. (New) The hydrogel according to claim 1 comprising at least 95% by weight pyrogen-free water or saline solution.

46. (New) The hydrogel according to claim 1, having a complex viscosity of about 2 to 50 Pas.

47. (New) The method according to claim 9, wherein the hydrogel has a complex viscosity of about 2 to 50 Pas.

Support for the amendments may be found throughout the application as originally filed, for instance on pages 5-6, and page 10, line 24 and in the claims as originally filed.

REMARKS

Claims 9-19 stand rejected under 35 U.S.C. §112 ¶ 1 as allegedly not being enabled. Claims 3-5, 7, 8, 11, 12, 14, 17, and 19 stand rejected under 35 U.S.C. §112 ¶ 2 as allegedly being indefinite. Claims 1-15, 18 and 19 stand rejected under 35 U.S.C. §103(a) as allegedly

being unpatentable over Vogel et al. (U.S. Patent 6,335,028), in view of Halpern et al. (U.S. 3,867,329). The rejections are respectfully traversed. Further the Applicant wishes to thank the Examiner for noting the improper dependent claim 17. It is believed that the objection has been corrected through amendment.

35 U.S.C. § 112 ¶ 1

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

On pages 2-4, the Examiner rejected claims 9-19 "because the specification, while being enabling for treating incontinence or vesicouretal reflux, does not reasonably provide enablement for preventing incontinence or vesicouretal reflux. The Applicant has amended the claims to recite "[a] method of treating."

Accordingly, Applicant believes that he has addressed the Examiner's concerns and rejections of the claims under 35 U.S.C. § 112, first paragraph.

Reconsideration and withdrawal of the rejections is respectfully requested.

Rejections Under 35 U.S.C. § 112 ¶2

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

On pages 4-5, Claims 3-5, 7, 8, 11, 12, 17, and 19 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for containing subject matter which fails to particularly point out and distinctly claim the invention.

More specifically, the Examiner states that the respective claims contain the language "preferably" and "such as" to indicate ranges which render the claims indefinite. The Applicant has amended the claims to more clearly define the desired ranges.

Accordingly, Applicant believes that he has addressed the Examiner's concerns and rejections of the claims under 35 U.S.C. § 112, second paragraph.

Reconsideration and withdrawal of the rejections is respectfully requested.

Rejection Under 35 U.S.C. § 103

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

On pages 5-6, the Examiner rejected claims 1-15, 18 and 19 under 35 U.S.C. §103(a) as allegedly being unpatentable over Vogel et al. (U.S. Patent 6,335,028) in view of Halpern et al. (U.S. 3,867,329).

The Examiner purports that Vogel et al. teach "a method for treating urinary incontinence by administering a pyrogen free composition and the composition comprises hydrophilic polyacrylamide or its derivatives and methylene-bis-acrylamide." The Examiner further states that it is known that the compositions of Vogel are hydrogels (citing Halpern et al.) and that the viscosity of the hydrogel composition would be easily measured by one skilled in the art. The Examiner alleges that one of ordinary skill in the art at the time of the invention "would have been motivated to prepare the composition of Vogel and administer it to treat urinary incontinence in a subject in need thereof." Office Action page 6.

Applicant respectfully disagrees and traverses this rejection.

As stated by the Federal Circuit, "a proper analysis under 35 U.S.C. § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). In addition, the prior art reference(s) must teach or suggest all of the claim limitations. The teaching or suggestion to combine and the reasonable expectation of success must both be found in the prior art, and not in Applicant's disclosure. *Id* at 493. *See also* M.P.E.P. § 2142.

Applicant initially notes that the present invention is directed toward a bio-stable hydrogel composition comprising the combination of acrylamide and methylene bis-acrylamide in amounts to provide about 0.5 to 25% by weight polyacrylamide, based on the total weight of

the hydrogel wherein said biostable hydrogel is in a form suitable for the treatment of incontinence and vesicouretal reflux and is substantially free of monomeric units.

Applicant submits that the claimed hydrogel's characteristics of being substantially free of monomeric units render patentable the claimed invention. Additionally, the Applicant provides further arguments which distinguish the claimed invention.

Contrary to the Examiner's assertions, one of ordinary skill in the art would not have a reasonable expectation of success in deriving Applicant's claimed invention from the cited references. While polyacrylamide gels have been widely used for various scientific practices, they are not typically biocompatible due to the toxic monomeric units that remain in the polymeric matrix. Vogel teaches the use of microbeads/microparticles in the treatment of urinary incontinence which preferably carry a positive charge on their surface. Conversely, the claimed hydrogel is substantially free of cationic units and thus not cationically charged (i.e., it is substantially neutral because it is substantially free of monomeric units). In contrast, Vogel teaches that his microparticles preferably contain a positive charge on the surface by way of a cationic monomer or polymer, directly teaching away from the Applicant's invention. (Col. 4, lines 35-38). Additionally, the gel of Vogel et al. is composed of microparticles of finite shape and size, while the gel of the claimed invention is more semi-fluid and its consistency is such that size and shape are not relevant parameters. Therefore, the claimed invention differs from Vogel et al. in both its chemical composition and its physical properties.

With regard to Halpern et al. Applicant notes that the gels of Halpern comprise an 80-90% polyacrylamide content (even more upon drying). (Col. 3, lines 48-53). Halpern's rods are designed to dilate a conduit *in vivo*. In contrast, the claimed invention contains about 0.5 to 25% polyacrylamide by weight and is designed to constrict a conduit *in vivo*.

Indeed, Vogel and Halpern both actually teach away from the claimed invention.

Further, it was stated in the Office Action, that "the viscosity of the hydrogel composition of the invention does not patentably distinguish the invention over the prior art." Applicant submits that the different characteristics of the gel may be critical to their intended purpose. (See Application page 10, lines 22-24). As such, viscosity is a patentable distinction, as it is a characteristic that can directly affect a gel matrix's ability to be suitable for its intended use. Therefore, patentable weight must be given to all the claim limitations including, "in a form

suitable for the treatment of incontinence and vesicouretal reflux and substantially free of monomeric units." (Claim 1).

Further with respect to viscosity, the viscosity recitations found in the dependent claims further distinguish the dependent claims from the references. It was conceded in the Office Action that Vogel fails to disclose the viscosity of his hydrogel composition, but it was alleged that "...one of ordinary skill in the art would know routine method of measuring/determining the viscosity of a hydrogel composition." (Office Action, page 6). While it may be correct that viscosity measurement is within knowledge of a person ordinarily skilled in the art, it does not mean that Vogel's copolymer has the Applicant's claimed viscosity or a viscosity which would have rendered obvious the Applicant's claimed viscosity. The burden remains on the Patent Office to show that Vogel would have suggested the various herein claimed viscosities.

The fact that a claimed product is within a broad field of the prior art and one might arrive at it by selecting specific items and conditions does not render the product obvious in the absence of some directions or reasons in the prior art for making such selections. *Ex parte Kuhn*, 132 U.S.P.Q. 359 (Pat. & Tr. Office Bd. App.)(1961). Similarly, in *In re Baird* the court recognized that a compound within the scope of a generic formula which encompasses more than 100 million compounds does not make obvious the motivation for the selection of specific compounds. (29 U.S.P.Q.2d 1550, (1994)). Indeed, in *In re Baird*, dissimilarly to the present situation the claimed invention was actually encompassed by the general formula of the prior art.

Prior art references in combination do not make an invention obvious unless something in the prior references would suggest the advantage to be derived from combining their teachings. *In re Sernaker*, 217 U.S.P.Q. 1, 6 (Fed. Cir. 1983). In the present case, the Examiner has done no more than find the separate elements of the present invention and argue that broad disclosures which would require specific selection and experimentation to achieve the current invention, render the present invention obvious.

A combination may be patentable whether it be composed of elements all new, partly new or all old. *Rosemont, Inc. v. Beckman Instruments, Inc.*, 221 U.S.P.Q. 1, 7 (Fed. Cir. 1984). There must be something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. *Lindemann v. Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 U.S.P.Q. 481, 488 (Fed. Cir. 1984). *Interconnect Planning Corporation v. Feil, et al.*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985). In the present case there is

no such motivation. One cannot pick and choose among individual parts of assorted references as a mosaic to recreate a facsimile of the claimed invention. *AKZO N.V. v. International Trade Commission*, 1 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1986). *Uniroyal v. Rudkin-Wiley*, 5 U.S.P.Q.2d 1434, 1438 (Fed. Cir. 1988).

If motivation were to exist, which it does not, one would not be motivated to select specific characteristics of Vogel et al.'s and Halpern et al.'s gels given their distinctly different designs with the expectation that they would provide a bio-stable hydrogel for the treatment of incontinence and vesicouretal reflux of the claimed invention. Further, one would not be motivated to utilize a gel substantially free of monomeric units, particularly since neither Halpern nor Vogel suggest that the final gel is substantially free of monomeric units. Indeed, the statutory standard of 35 U.S.C. §103 is whether the invention, considered as a whole, would have been obvious to one of ordinary skill in the art, not whether it would have been obvious for one of ordinary skill in the art to try various combinations. *Akzo N.V. v. E.I. duPont de Nemours*, 1 U.S.P.Q.2d 1705, 1707 (Fed. Cir. 1987). Where the prior art discloses no particular preference for the component claimed from among a number of other components disclosed in a reference, i.e., where there is no disclosure within the prior art that would have led the routineer to make the critical selections to arrive at the claimed composition, the court found a rejection for obviousness could not be sustained. *Ex parte Wittpenn*, 16 U.S.P.Q.2d 1730, 1731 (PBAI 1990).

Each of the claims 2-8 and 10-41 are dependent claims on claims 1 and 9, and therefore incorporate all of the limitations of Claim 1 and 9 in addition to the further limitations set forth in the dependent claims at issue. As stated above, a proper *prima facie* obviousness rejection requires that the prior art reference(s) must teach or suggest all of the claim limitations. For the reasons set forth above, Vogel *et al.* in view of Halpern *et al.* does not render obvious the claims. As stated in the M.P.E.P., "[i]f an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious." *See* M.P.E.P. § 2143.03 (citing *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988)).

Reconsideration and withdrawal of the rejections is respectfully requested.

Conclusion

Applicant believes that for all the reasons detailed above all claims in this application are in a condition for allowance. Early notification of a favorable consideration is respectfully requested.

In the event any outstanding issues remain, Applicant would appreciate the courtesy of a telephone call from the Examiner to resolve any such issues in an expeditious manner to place the application in condition for allowance.

Respectfully submitted,

HUNTON & WILLIAMS

Date: August 13, 2002

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Attachment A

IN THE SPECIFICATION:

I. On Page 1, lines 6-10.

Polyacrylamide hydrogels are used herein as endoprosthetic devices for bulking the urethra, rectum or colon (or *canalis analis*), or ureter in order to increase resistance in these conduits for the treatment of urinary incontinence, anal incontinence, and vesicouretal reflux. The polyacrylamide hydrogels comprises 0.5 to 25% by weight polyacrylamide and either pyrogen-free water or saline solution.

II. On Page 1, lines 26-31.

Vesicouretal reflux is the result of decreased ureteral resistance wherein urine from the bladder refluxes back into the kidney. This can result in the transport of bacteria ~~form~~ from the bladder back up through the ureter, clayceal dilation, the renal pyramids and the kidneys and may lead to infections and recurrent pyelonephritis as well as cause physiological injury to the renal parenchyma. This may lead to renal failure.

III. On Page 3, lines 21-25.

A first aspect of the invention relates to a bio-stable hydrogel for use ~~in the~~ in the treatment and prevention of incontinence and vesicouretal reflux, said hydrogel obtainable by combining acrylamide and methylene bis-acrylamide in amounts so as to give about 0.5 to 25% by weight polyacrylamide, based on the total weight of the hydrogel; radical initiation; and washing with pyrogen-free water or saline solution.

IV. On Page 4, lines 1-5.

An important object of the invention is to provide a prosthetic device for increasing the resistance of conduits selected from the group consisting of the urethra; the rectum or colon; and the ureter for the treatment of urinary incontinence, anal incontinence, and vesicouretal reflux, respectively; wherein said device is injectable and ~~comprising~~ comprises the bio-stable hydrogel of the invention.

V. On Page 4, lines 11-22.

A first aspect of the invention relates to the bio-stable hydrogel obtainable by combining acrylamide and methylene bis-acrylamide in amounts so as to give about 0.5 to 25% by weight polyacrylamide, based on the total weight of the hydrogel; radical initiation; and washing with pyrogen-free water or saline solution, for use ~~in the~~ in the treatment and prevention of incontinence and vesicouretal reflux. The bio-stable hydrogel typically has a molecular weight between 0.01×10^6 and 20×10^6. The polymer is resistant to biological degradation and is not permeable through biological membranes. The polyacrylamide hydrogel of the invention is fully biocompatible (according to ISO standard test ISO-10993). The polyacrylamide hydrogel does not have cytotoxic effect on human fibroblasts, is non-toxic, non-carcinogenic, non-allergenic, non-mutagenic, and resistant to enzymatic and microbiological degradation. Furthermore, the polymer is not water-soluble.

VI. On page 5, lines 26-30.

The device also has elastic properties due to, at least in part of the high water binding capacity of the hydrogel of water. This is of great relevance in terms, at least, of

durability and ability to provide resistance through the conduit. In a preferred embodiment, the hydrogel of the invention has an elasticity modulus of about 1 to 200 Pa, such as about 2 to 175 Pa, typically about 5 to 150 Pa, such as 10 to 100 Pa.

VII. On page 14, line 10.

g) pre-~~eash~~ wash values - washing typically reduces value by 20-40%

VIII. On page 17, lines 1-5.

The medical procedure involves injection of polyacrylamide gel under the mucous membrane of the uretha of women suffering from incontinence. Injection is via the external surface of the urethra and toward the submucosal membrane. 3 mL are injected at three depots sites ~~are~~ made along a single longitudinal position of the urethra. Depots 0.5 cm distally from the neck of the bladder were made.

IN THE CLAIMS:

1. (Amended) A bio-stable hydrogel ~~for use in the in the treatment and prevention of incontinence and vesicouretal reflux said hydrogel obtainable by combining~~comprising the combination of acrylamide and methylene bis-acrylamide in amounts ~~so as~~ to ~~give~~ provide about 0.5 to 25% by weight polyacrylamide, based on the total weight of the hydrogel~~; radical initiation; and washing with pyrogen free water or saline solution~~ wherein said biostable hydrogel is in a form suitable for the treatment of incontinence and vesicouretal reflux and is substantially free of monomeric units.~~.~~

2. (Amended) The hydrogel according to claim 1, wherein said ~~combining~~ combination of acrylamide and methylene bis-acrylamide ~~is in~~is obtained by combining the acrylamide and the methylene bis-acrylamide in a molar ratio of 150:1 to 1000:1.

3. (Amended) The hydrogel according to claim 1, comprising less than 15% by weight polyacrylamide, based on the total weight of the hydrogel. ~~, preferably less 10%, more preferably less than 7.5%, even more preferably less than 5%, most preferably less than 3.5% % by weight polyacrylamide, based on the total weight of the hydrogel.~~

4. (Amended) The hydrogel according to claim ~~3~~1, comprising at least 1% by weight polyacrylamide, based on the total weight of the hydrogel. ~~, preferably at least 1.5%, such as 1.6% % by weight polyacrylamide, based on the total weight of the hydrogel.~~

5. (Amended) The hydrogel according to claim 1, having a complex viscosity ~~module~~ of about ~~2 to 50 Pas, such as about~~ 2 to 40 Pa-s. ~~, preferably about 2 to 30 Pa-s, more preferably about 2 to 20 Pa-s.~~

6. (Amended) The hydrogel according to claim 1, for use in the ~~in the~~ treatment ~~and prevention~~ of incontinence.

7. (Amended) The hydrogel according to claim ~~1~~42, further comprising at least 75% by weight pyrogen-free water or saline solution. ~~, preferably pyrogen-free water.~~

8. (Amended) The hydrogel according to claim 7 comprising at least 80% by weight pyrogen-free water or saline solution. ~~, preferably at least 85 %, more preferably at least 90%, even more preferably at least 95% by weight pyrogen-free water or saline solution.~~

9. (Amended) A method of treating ~~or preventing~~ incontinence or vesicouretal reflux comprising administering a hydrogel to a mammal, said hydrogel comprising 0.5 to 25% by weight polyacrylamide, based on the total weight of the hydrogel and is substantially free of monomeric units.

11. (Amended) The method according to claim 9, wherein the hydrogel comprises less than 15% by weight polyacrylamide, based on the total weight of the hydrogel~~,~~ ~~preferably less 10%, more preferably less than 7.5%, even more preferably less than 5%, most preferably less than 3.5% % by weight polyacrylamide, based on the total weight of the hydrogel.~~

12. (Amended) The method according to claim 11, wherein the hydrogel comprises at least 1% by weight polyacrylamide, based on the total weight of the hydrogel~~,~~ ~~preferably at least 1.5%, such as 1.6% % by weight polyacrylamide, based on the total weight of the hydrogel.~~

13. (Amended) The method according to claim 9, wherein the hydrogel has a complex viscosity of about ~~2 to 50 Pas, such as about~~ 2 to 40 Pas~~,~~ ~~such as about 2 to 30 Pas. preferably about 2 to 20 Pas.~~

14. (Amended) The method according to claim 9, wherein the hydrogel comprises at least 80% by weight pyrogen-free water or saline solution~~,~~ ~~preferably at least 85 %, more preferably at least 90%, even more preferably at least 95% by weight pyrogen-free water or saline solution~~

16. (Amended) The method according to claim 15, wherein the injecting of the hydrogel comprises injections ~~selected from the group consisting of~~ which include
injections at positions 10, 2, and 6 o'clock of the cross-sectional axis of the urethra for the treatment of urinary incontinence;
injections at positions 10, 2, and 6 o'clock of the cross-sectional axis of the colon or rectum for the treatment of anal incontinence; ~~and~~or
injections at positions 10, 2, and 6 o'clock of the cross-sectional axis of the ureter for the treatment of vesicouretal reflux.

17. (Amended) The method according to ~~any one of~~ claim~~s~~ 9, further comprising the ~~use~~ inclusion of cells, ~~such as stem cells for cellular engraftment to the surrounding tissue in the ureter, urethra or *analis canalis.*~~

18. A prosthetic device for increasing the resistance of conduits comprising ~~selected from the group consisting of the~~ a urethra~~;~~, ~~the~~ a rectum, ~~or~~ a colon~~;~~, ~~and the~~or a ureter ~~for the treatment of urinary incontinence, anal incontinence, and vesicouretal reflux, respectively;~~

wherein said device is injectable and comprise~~s~~ing a hydrogel as defined in any of claims 1 to 8.

19. (Amended) The device according to claim 18, further comprising cells, ~~such as stem cells for cellular engraftment to the surrounding tissue in the ureter, urethra or *analis canalis.*~~

20. (New) The hydrogel according to claim 1, comprising less than 10% by weight polyacrylamide, based on the total weight of the hydrogel.

21. (New) The hydrogel according to claim 1, comprising less than 7.5% by weight polyacrylamide, based on the total weight of the hydrogel.

22. (New) The hydrogel according to claim 1, comprising less than 5% by weight polyacrylamide, based on the total weight of the hydrogel.

23. (New) The hydrogel according to claim 1, comprising less than 3.5% by weight polyacrylamide, based on the total weight of the hydrogel.

24. (New) The hydrogel according to claim 1, comprising at least 1.5% by weight polyacrylamide, based on the total weight of the hydrogel.

25. (New) The hydrogel according to claim 1, comprising at least 1.6% by weight polyacrylamide, based on the total weight of the hydrogel.

26. (New) The hydrogel according to claim 1, having a complex viscosity of about 2 to 30 Pas.

27. (New) The hydrogel according to claim 1, having a complex viscosity of about 2 to 20 Pas.

28. (New) The biostable hydrogel composition of claim 42, wherein washing is done with pyrogen-free water.

29. (New) The method according to claim 9, wherein the hydrogel comprises less than 10% by weight polyacrylamide, based on the total weight of the hydrogel.

30. (New) The method according to claim 9, wherein the hydrogel comprises less than 7.5% by weight polyacrylamide, based on the total weight of the hydrogel.

31. (New) The method according to claim 9, wherein the hydrogel comprises less than 5% by weight polyacrylamide, based on the total weight of the hydrogel.

32. (New) The method according to claim 9, wherein the hydrogel comprises less than 3.5% by weight polyacrylamide, based on the total weight of the hydrogel.

33. (New) The method according to claim 9, wherein the hydrogel comprises at least 1.5% by weight polyacrylamide, based on the total weight of the hydrogel.

34. (New) The method according to claim 9, wherein the hydrogel comprises at least 1.6% by weight polyacrylamide, based on the total weight of the hydrogel.

35. (New) The method according to claim 9, wherein the hydrogel has a complex viscosity of about 2 to 30 Pas.

36. (New) The method according to claim 9, wherein the hydrogel has a complex viscosity of about 2 to 20 Pas.

37. (New) The method according to claim 17, wherein the cells comprise stem cells.

38. (New) The method according to claim 17, wherein the cells allow for cellular engraftment to the surrounding tissue in the ureter, urethra or *analis canalis*.

39. (New) The device according to claim 19, wherein the cells include stem cells.

40. (New) The device according to claim 19, wherein the cells allow for cellular engraftment to the surrounding tissue in the ureter, urethra or *analis canalis*.

41. (New) The device according to claim 18, wherein the device increases the resistance of the urethra to treat urinary incontinence, increases the resistance of the rectum or colon to treat anal incontinence or increases the resistance of the ureter to treat vesicouretal reflux.

42. (New) The hydrogel according to claim 1 which is made under the conditions of radical initiation and washing with pyrogen-free water or saline solution.

43. (New) The hydrogel according to claim 42 comprising at least 85% by weight pyrogen-free water or saline solution.

43. (New) The hydrogel according to claim 1 comprising at least 90% by weight pyrogen-free water or saline solution.

45. (New) The hydrogel according to claim 1 comprising at least 95% by weight pyrogen-free water or saline solution.

46. (New) The hydrogel according to claim 1, having a complex viscosity of about 2 to 50 Pas.

47. (New) The method according to claim 9, wherein the hydroget has a complex viscosity of about 2 to 50 Pas.

ABSTRACT

The present invention relates to a bio-stable hydrogel for use in the treatment and prevention of incontinence and vesicouretal reflux. The hydrogel is obtainable by combining acrylamide and methylene bis-acrylamide in amounts to provide about 0.5 to 25% by weight polyacrylamide, based on the total weight of the hydrogel.